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EXAMINER	
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte BERISLAV V. ZLOKOVIC,
Appellant[1]

Appeal 2010-002106
Application 10/516,729
Technology Center 1600

Decided: March 23, 2010

Before CAROL A. SPIEGEL, FRANCISCO C. PRATS, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

SPIEGEL, *Administrative Patent Judge*.

DECISION ON APPEAL

Appellant appeals under 35 U.S.C. § 134 from an Examiner's final rejection of claims 1, 2, 5, 6, and 27-40 as amended on June 12, 2008. Claims 7-26, the only other pending claims, are withdrawn from

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[1] The real parties-in-interest are The University of Rochester and Socratech, L.L.C. (Brief For Appeal Under 37 CFR § 41.37 filed 23 June 2009 (hereinafter "Br.") at 1-2).

consideration as directed to nonelected inventions. (Br. 2; Ans.[2] 2.) We have jurisdiction under 35 U.S.C. § 134. We REVERSE.

STATEMENT OF THE CASE

The subject matter on appeal is directed to methods of assaying for vascular dysfunction in a human patient affected by a neurodegenerative disorder or other cognitive impairment, such as Alzheimer's disease (hereinafter "AD"), by determining whether there is inappropriate cellular senescence and/or defective angiogenesis in the patient's endothelial cells. Claim 1 is illustrative and reads (Br. 9):

> 1. A method of assaying for vascular dysfunction in a human subject affected by a neurodegenerative disorder or another cognitive impairment, said method comprising:
> (a) obtaining endothelium or cells derived from endothelium of said human subject,
> (b) culturing endothelial cells therefrom, and
> (c) determining whether there is inappropriate senescence and/or defective angiogenesis in at least said endothelial cells which is indicative of vascular dysfunction in said human subject.

The Examiner has rejected claims 1, 2, 5, 6, and 27-40 as unpatentable under 35 U.S.C. § 103(a) over the combined teachings of Grammas[3] and Mulliken[4] (Ans. 3-5).[5] According to Appellant, claims 1, 2, 5, 6, and 27-40

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[2] Examiner's Answer mailed 12 August 2009 (hereinafter "Ans.").
[3] Grammas et al., *Alzheimer Disease Amyloid Proteins Inhibit Brain Endothelial Cell Proliferation in vitro*, 6 DEMENTIA 126-130 (1995) (hereinafter "Grammas").
[4] Mulliken et al., *In vitro characteristics of endothelium from hemangiomas and vascular malformations*, 92 SURGERY 348-353 (1982) (hereinafter "Mulliken").

stand or fall together (Br. 5). Therefore, we decide this appeal on the basis of claim 1. 37 C.F.R. § 41.37(c)(1)(vii).

The Examiner found that Grammas teaches contacting cultured rat cerebral endothelial cells with ß-amyloid (hereinafter "Aß") from human Alzheimer's patients, but does not teach obtaining and culturing human endothelial cells from Alzheimer's patients or subsequently determining the degree of defective angiogenesis as encompassed by claim 1 (Ans. 3). The Examiner found that Mulliken teaches obtaining and culturing human hemangiomas, which comprise vascular endothelium and subsequently undergo tube-formation *in vitro*, i.e., *in vitro* angiogenesis (*id.* at 3-4). The Examiner concluded that it would have been obvious

> to modify the methods of Grammas to include the step of culturing human endothelial cells derived from the brain, as taught by Mulliken . . . and determine the degree of defective angiogenesis . . . to determine the degree of defective angiogenesis and endothelial cell proliferation in the same tissue from the same species of mammal as Grammas had already obtained human brain samples from 8 Alzheimer patients (page 127). It would be reasonable to expect success . . . [because] Grammas indicates that Aß from human Alzheimer's patients results in defective proliferation of endothelial cells from blood vessels (i.e., angiogenesis), and . . . Mulliken teaches that it is routine to culture endothelial cells from human tissue and . . . that this method shows the changes in endothelial cells phenotypes.

(*Id.* at 4.) According to the Examiner, modifying Grammas in this manner "merely recite[s] features of the cells which are necessarily present" (*id.*).

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[5] The Examiner withdrew the final rejections of claims 1, 3, 5, 6, and 39 following entry of an after-final Amendment submitted on 12 June 2008 in an Advisory Action mailed 2 July 2008 (Br. 2; Ans. 2).

Appellant argues that neither Grammas nor Mulliken teach culturing endothelium or endothelial cells from diseased subject, i.e., a human affected by a neurodegenerative disorder or another cognitive impairment (Br. 6). Appellant further argues that Grammas teaches culturing endothelial cells to determine the toxic effects of Aß on normal cells and, therefore, fails to provide a reason to assay endothelial cells from a human affected by a neurodegenerative disorder or another cognitive impairment for vascular dysfunction (*id.* at 6-7).

Therefore, at issue is whether the combined teachings of Grammas and Mulliken would have provided a reason for one of ordinary skill in the art to substitute endothelium or endothelial cells obtained from a human affected with AD in place of the normal rat cerebral endothelial cells in the method of Grammas and to further determine whether defective angiogenesis existed in the cultured human cells in order to assay for vascular dysfunction with a reasonable expectation of success.

FINDINGS OF FACT

The following findings of fact are supported by a preponderance of the evidence of record.

A. Grammas

[1] According to Grammas,

> [a] connection between the vasculature and AD lesions is suggested by a significant reduction in vascular density and capillary diameter as well as deformities of angioarchitecture [the arrangement and distribution of blood vessels in an organ] in AD. Accumulation of Aß in blood vessels causes degeneration of endothelial and smooth muscle cells and thus could underlie changes in cerebral blood flow and vascular rupture.

(Grammas 126, ¶ 1.)

[2] In particular, Grammas plated 1 x 10^4 rat cerebral endothelial cells/well with and without (i) AD plaques (obtained from post mortem human brains) or (ii) synthetic amyloid proteins, trypsinized the cultures after one day, and counted the number of cells that survived (Grammas 127, ¶¶ 2-3 and 5-6).

[3] Grammas found that AD plaques, but not synthetic $A\beta_{1-40}$, inhibited endothelial cell proliferation (Grammas 129, ¶ 2).

[4] Grammas noted that AD plaques contain (i) minor components that potentiate amyloid toxicity in culture, (ii) $A\beta_{1-40}$, and (iii) the longer amyloid peptide $A\beta_{1-42}$ which has undergone posttranslational modifications making it chemically distinct from synthetic $A\beta_{1-40}$ (Grammas 129, ¶ 2).

[5] According to Grammas, "amyloid proteins, although not directly toxic to brain endothelial cells, could compromise vascular cell function and potentially contribute to an impaired blood-brain barrier in AD," but several questions remain to be answered, e.g., whether brain endothelial cells are selectively susceptible to AD plaques and what role endothelial heterogeneity plays in response to amyloid proteins (Grammas 129, ¶ 3).

C. Mulliken

[6] Mulliken compared the *in vitro* characteristics of endothelium from hemangiomas (vascular tumors with increased endothelial turnover and increased numbers of mast cells during the proliferative phase) and vascular malformations (vascular anomalies with normal

endothelial cells cycle and normal mast cell counts) (Mulliken 348, ¶ 1).

[7] In particular, Mulliken grew endothelial cells into colonies, trypsinized them after 2 to 3 weeks, and examined the colonies by light microscopy (Mulliken 348-350, "Cell culture").

[8] Specifically, capillary endothelial cells from three of four hemangiomas grown in medium essential for tubule formation formed capillary tubes – "'angiogenesis in vitro'" – usually within 1 or 2 months after the first culture (Mulliken 350, ¶ 4).

[9] However, capillary endothelium from four malformations was difficult to culture and none of the three cultures placed in stimulatory medium formed tubules (Mulliken 351, ¶ 2).

[10] According to Mulliken, "[i]t is not known if hemangioma growth is due to external stimulus, the deficiency of an inhibitor, or an intrinsic defect in the endothelium" (Mulliken 351, ¶ 6).

LEGAL PRINCIPLES

The question of obviousness is resolved on the basis of underlying factual determinations including (1) the scope and content of the prior art, (2) any differences between the claimed subject matter and the prior art, (3) the level of skill in the art, and (4) wherein in evidence, so-called secondary considerations. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966). In *KSR*, the Supreme Court emphasized that "'[r]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (citing *In re Kahn*, 441 F.3d 977,

988 (Fed. Cir. 2006)). Furthermore, "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." *KSR*, 550 U.S. at 421. In particular, a claim directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each element was, independently, known in the prior art." *Id.* at 401. Finally, obviousness under § 103 requires a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988).

ANALYSIS

We note that the prior art acknowledges that human AD patients show a significant reduction in vascular density and capillary diameter as well as deformities of angioarchitecture (FF 1). However, the issue before us is whether the combined teachings of Grammas and Mulliken would have provided a reason for one of ordinary skill in the art to substitute endothelium or endothelial cells obtained from a human affected with AD in place of the normal rat cerebral endothelial cells used by Grammas and to further determine whether defective angiogenesis existed in the cultured human cells in order to assay for vascular dysfunction with a reasonable expectation of success.

It stands to reason that cerebral endothelial cells in a human diagnosed with AD would have already been exposed to Aß plaque proteins by virtue of the diagnosed AD. In Grammas' assay, normal rat cerebral endothelial cells are cultured with Aß proteins in order to ascertain the effect of the Aß proteins on the cells (FF 2). Thus, it is unclear why one of ordinary skill in the art would have cultured cells that have already been exposed to Aß proteins to additional Aß proteins to see what effect exposure to Aß proteins

has on the cells. Moreover, it is unclear how one of ordinary skill in the art would have separated a post-post-Aß proteins exposure effect from a post-Aß proteins exposure effect.

It is also unclear why one of ordinary skill in the art would have further modified the method of Grammas to determine the degree of defective angiogenesis as suggested by the Examiner. While the Examiner's statement that proliferation of endothelial cells derived from blood vessels is required for angiogenesis (Ans. 3) is unchallenged, Mulliken teaches that not all vascular endothelial cells will form capillary tubes, i.e., undergo "'angiogenesis in vitro,'" even when grown in medium designed to stimulate tubule formation (FF 8-9). Thus, the Examiner has not explained how the combined teachings of the prior art provides a reasonable expectation of successfully culturing cerebral endothelial cells to form capillary tubes, e.g., why cerebral endothelial cells are more like hemangioma endothelial cells than vascular malformation endothelial cells. Indeed, Mulliken does not know if hemangioma growth is due to external stimulus, deficiency of an inhibitor, or an intrinsic defect in the endothelium (FF 10). Therefore, it seems that the Examiner has fallen into the trap of hindsight reconstruction.

CONCLUSION

Therefore, we will reverse the rejection of claims 1, 2, 5, 6, and 27-40 under § 103(a) over the combined teachings of Grammas and Mulliken. In our view, the combined teachings of Grammas and Mulliken would not have provided a reason for one of ordinary skill in the art to substitute endothelium or endothelial cells obtained from a human affected with AD in place of the normal rat cerebral endothelial cells used in the method of Grammas or to further determine whether defective angiogenesis existed in

the cultured human cells in order to assay for vascular dysfunction with a reasonable expectation of success.

ORDER

Upon consideration of the record, and for the reasons given, it is ORDERED that the decision of the Examiner rejecting claims 1, 2, 5, 6, and 27-40 as unpatentable under 35 U.S.C. § 103(a) over the combined teachings of Grammas and Mulliken is REVERSED.

REVERSED

cdc

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